Indomethacin Therapy for Hypertrophic Pulmonary Osteoarthropathy in Patients With Bronchogenic Carcinoma

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Hypertrophic pulmonary osteoarthropathy (HPO) is a disabling complication of lung cancer often requiring thoracotomy with vagotomy for control of pain. This condition was confirmed by scintigraphy in six consecutive patients with biopsy-proved lung cancer. All had characteristic bone and joint pain unresponsive to a variety of analgesics. Treatment with indomethacin gave dramatic relief of pain within 72 hours in all six. Consideration should be given to instituting a controlled trial to establish the efficacy of indomethacin for the treatment of HPO.

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Hypertrophic pulmonary osteoarthropathy (HPO) is a disabling complication of lung cancer often requiring thoracotomy with or without vagotomy for control of bone pain.[1] Six consecutively seen patients were treated with indomethacin for the pain of HPO. We report our experience and review the literature to offer a rationale for this form of therapy and, in addition, document the effect of indomethacin on the bone scan findings in cases of HPO.

Methods

Over a two-year period from 1979 to 1981, six patients presented to Wadsworth VA Medical Center with arthralgia, bone pain and abnormal findings on chest radiographs, diagnosed as HPO. The patients were treated with indomethacin. In addition to a history and physical examination, radiographs of the symptomatic extremities were taken, together with a radionuclide bone scan before treatment. Lung cancer was confirmed by bronchoscopic or aspiration biopsy. Treatment with indomethacin was initiated at 25 mg three times a day and increased to 50 mg three times a day if there was no symptomatic improvement after 24 hours. The bone scan was repeated in the last three of these six patients at 4, 12 and 16 days after starting indomethacin therapy. Follow-up data, including any change in arthralgia or bone pain, and the results of thoracotomy were recorded.

Results

These six patients were all men, aged from 46 to 62 years. Their smoking history ranged from 40 to 100 pack-years. Four had adenocarcinoma and two had epidermoid carcinoma of the lung. In four patients, the bone pain preceded the diagnosis of lung cancer by one to three months. In two patients, bone pain, pulmonary symptoms and abnormalities on a chest radiograph were recognized at about the same time. The most common bone symptom was a deep-seated ankle and shin pain reported by all six patients. Other joints frequently involved were the knees and the wrists. Clubbing of the fingers was present in five patients. Nonpitting edema of varying degrees over the involved joints was present in all six patients, and two had unmistakable knee effusions. Radiographs of the long bone showed characteristic periosteal elevations in five of the six. One patient had normal-appearing long bone on x-ray films. However, the bone scan was positive in all six patients (Figure 1).

Before admission, analgesics, including aspirin, acetaminophen or codeine, were tried by these patients, with only minor relief of bone pain. These treatments were not repeated in hospital. Two patients were treated with 25 mg and four patients with 50 mg of indomethacin given three times a day. Significant relief of bone pain occurred within 24 hours in two, 48 hours in another three and 72 hours in the sixth patient. The bone scan was repeated in the last three of these

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six patients at 4, 12 and 16 days after starting indomethacin therapy. All three repeat bone scans remained positive. Five patients underwent exploratory thoracotomy. Four underwent resection of lung tumors. Vagotomy was not done in any patient. All five patients had resolution of bone pain after thoracotomy, so that therapy with indomethacin did not need to be restarted. The one patient not operated on was treated with radiation therapy. Bone pain persisted and continued use of indomethacin was necessary.

Discussion

In this uncontrolled study of six consecutive patients with HPO due to lung cancer, indomethacin in doses of 25 to 50 mg three times a day rapidly and completely controlled the disabling bone pain. There is indirect evidence that prostaglandins may be involved in the pathogenesis of this condition. The plasma concentrations of prostaglandins $F_2\alpha$ and E are significantly higher in cystic fibrosis patients with digital clubbing than in those without clubbing.[2] In vitro organ culture studies have shown that prostaglandins can cause an increase in number and activity of osteoclasts[3] and an increase in bone resorption.[4] In vivo, both are prerequisites to the new bone formation that is the hallmark of HPO.[5] Indomethacin was chosen for study because it has been shown to inhibit such new bone formation in a variety of conditions, perhaps as a result of prostaglandin synthesis inhibition,[6] such as Haversian remodeling in rabbits,[7] ectopic ossification after a hip operation,[8] fracture healing in rats[9] and bone resorption in periodontitis in dogs.[10] In addition, there are several anecdotal reports of the effective use of indomethacin in cases of HPO.[11-13]

The documented efficacy of other analgesics such as aspirin,[14] which is also a prostaglandin synthetase inhibitor, further supports the possibility that prostaglandins may be important in the pathogenesis of the pain symptom of HPO. A double-blind controlled study would be desirable to firmly establish the efficacy of this treatment in patients with HPO. Whether this treatment may be useful as a diagnostic tool in the evaluation of long bone pain in which radiographic evidence of periostitis is absent deserves further study. In practice, complaints of long bone pain are common in conditions such as osteomalacia, discogenic disease, soft tissue rheumatism, infections and venous insufficiency, but in general such pain does not respond to indomethacin therapy as rapidly as in patients with HPO. The rapid relief of pain noted in this study could be used to raise the possibility of HPO, and the diag-

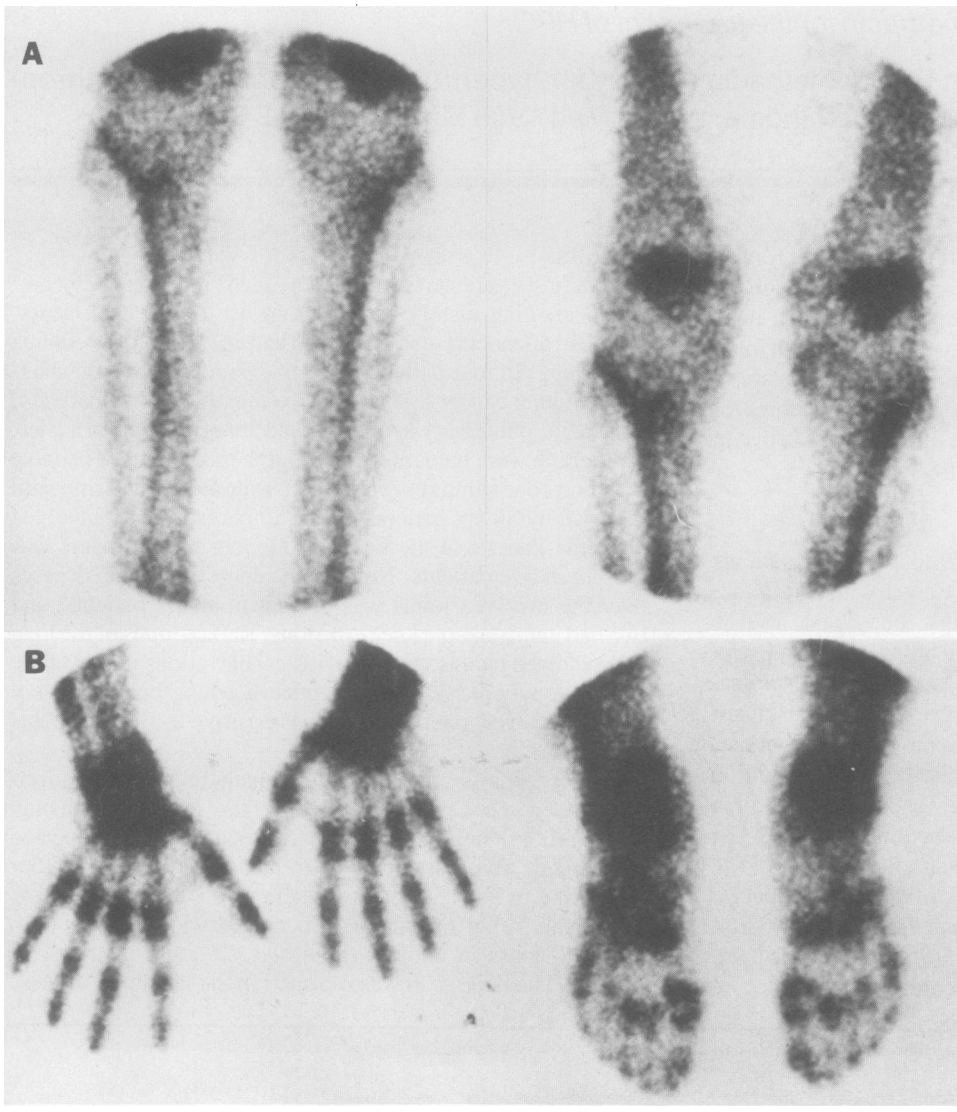

Figure 1.—A, radionuclide bone scan of part of the femur and tibia showing diffuse, symmetrically increased cortical uptake of technetium Tc 99m medronate (the "parallel tract" sign). **B,** Similar scan of the hands and feet, with considerable uptake in wrists, ankles and digits.

nosis then would be confirmed easily by bone scan. Bone scanning has been shown to be more sensitive than routine bone radiographs in recording the full extent of skeletal involvement,[15,16] though it has not been recommended as a diagnostic tool. The results have been shown to revert to normal one month after appropriate treatment of a lung tumor or metastasis, whereas bone radiographs continue to show abnormalities[16-18] and we were interested to further define the time course of this change. In this study, bone scans were uniformly positive, confirming the sensitivity of the test. In this situation bone scans may allow an earlier diagnosis of HPO and consequently an earlier search for an occult lung cancer. There have been reports of bone scan findings returning to normal 1 to 12 months following definitive treatment of a case of lung cancer. In our experience, however, the scans that were repeated within two weeks showed findings that were unchanged.

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